

# Model-based sensor of hemodynamics in critical care

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## Abstract

A model-based approach for real time tracking of key hemodynamic parameters in a porcine model of pulmonary embolism is presented. The model and methods are clinically validated by successfully capturing a significantly wide range of dynamics and reproducing all the physiological correct responses. The mean prediction errors were at most 4.1% in the pressures and 3.1% in the volumes for 6 sets of clinical data. Pulmonary resistance was found to rise dramatically in all cases with total increases ranging from 90 – 261%. The septum volume significantly decreased corresponding to a movement of the right ventricle to the left, consistent with accepted hemodynamic response to pulmonary embolism. The model correctly predicts right ventricular-vascular decoupling and compares well to a similar highly invasive measure based on rapid inferior vena cava occlusion manoeuvre. The results show the potential for real-time sensor integration in critical care where common pressure and volume measurements can be aggregated into a simpler form that more directly points to cardiac disease states and assists in optimum therapy selection.

**Keywords:** Cardiac model, hemodynamic sensor, right ventricular-vascular coupling, pulmonary embolism

## 1 Introduction

Cardiac disease state is highly patient specific and difficult to accurately diagnose due to the limited measurements available and the body's natural reflex responses to restore circulatory equilibrium, which can often mask the underlying symptoms. Hence successful diagnosis and treatment often rely on the experience and intuition of clinical staff.

This research employs a physiologically validated minimal model [1], and uses a patient specific modelling methodology previously developed in simulation [2, 3], to better aggregate continuously measured hemodynamic responses into a more direct picture of a patient's condition. This paper validates the approach on a porcine model of pulmonary embolism. The time varying dynamics of important hemodynamic variables like pulmonary resistance, ventricular contractility and right ventricle expansion index are computed using the model-based approach. The model-based approach therefore effectively integrates common pressure and volume sensors in the ICU into a more clinically useful form, to better assess the cardiac state of patients.

For example, an important feature in the CVS, not easily measured, is a dynamic called right ventricular-vascular coupling. When the afterload of the right ventricle increases, the heart has a natural reflex response to increase right ventricular contractility to maintain cardiac output. The ventricular contractility is therefore considered to be coupled to the afterload. The afterload can be simply thought of as the pulmonary

vascular resistance.

Due to the natural coupling mechanism, clinical signs of heart failure are not clearly related to the progression of pulmonary artery pressure and resistance alone [4]. In porcine models of septic shock, a common cardiac disease state in the Intensive Care Unit (ICU), coupling is preserved even with quite significant increases in pulmonary pressure [5]. In conditions of acute pulmonary hypertension, ventricle failure results from decoupling of the contractility from its afterload [5, 6].

Continuous monitoring of coupling in ICU patients is readily achieved using the patient specific cardiac modelling methodologies in this paper. Furthermore, the model-based coupling measure compares very well to the traditionally highly invasive measure based on the rapid inferior vena cava occlusion maneuver. This maneuver involves inserting a balloon catheter in the vena cava and opening it up for short bursts to measure the pressure volume response [4]. Overall, the porcine pulmonary embolism experiments provide an important first step towards model-based CVS management in the ICU.

## 2 Methodology

### 2.1 CVS model

The CVS model is a lumped parameter model similar to [1], where the left and right ventricle chambers are characterized by the flow in and out of the chamber, the pressure up- and downstream and the resistances of the valves, and inertia of the blood. An overview of the

model is given in Figure 1.

The equations for the left ventricle are defined:

$$V_{pcd} = V_{lv} + V_{rv} \quad (1)$$

$$P_{pcd} = P_{0,pcd} \cdot (e^{\lambda_{pcd}(V_{pcd}-V_{0,pcd})} - 1) \quad (2)$$

$$P_{peri} = P_{pcd} + P_{th} \quad (3)$$

$$V_{lvf} = V_{lv} - V_{spt} \quad (4)$$

$$P_{lvf} = dri_L \cdot E_{es,lvf} \cdot (V_{lvf} - V_{d,lvf}) + (1 - dri_L) \cdot P_{0,lvf} \cdot (e^{\lambda_{lvf}(V_{lvf}-V_{0,lvf})} - 1) \quad (5)$$

$$P_{lv} = P_{lvf} + P_{peri} \quad (6)$$

$$P_{pu} = E_{pu} \cdot (V_{pu} - V_{d,pu}) + P_{th} \quad (7)$$

$$\dot{V}_{ao} = Q_{av} - Q_{sys} \quad (8)$$

$$Q_{sys} = \frac{P_{ao} - P_{vc}}{R_{sys}} \quad (9)$$

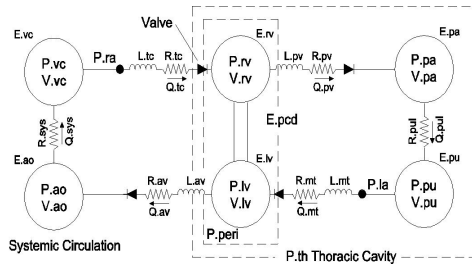
$$P_{ao} = E_{ao} \cdot (V_{ao} - V_{d,ao}) \quad (10)$$

$$\dot{V}_{lv} = Q_{av} - Q_{mt} \quad (11)$$

$$\dot{Q}_{mt} = H(H(P_{pu} - P_{lv}) + H(Q_{mt})) \cdot \frac{(P_{pu} - P_{lv} - R_{mt} \cdot Q_{mt})}{L_{mt}} \quad (12)$$

$$\dot{Q}_{av} = H(H(P_{lv} - P_{ao}) + H(Q_{av})) \cdot \frac{(P_{lv} - P_{ao} - R_{av} \cdot Q_{av})}{L_{av}} \quad (13)$$

where  $H$  is the Heaviside function,  $dri_L$  is the left ventricle driver function (see below) and all other variables are as shown in Figure 1. Similar equations are used for the right ventricle and pulmonary/systemic circulation. For a more detailed description see [1,2,7].



**Figure 1:** Minimal CVS model overview

### 2.1.1 Activation Function and Ventricular Interaction

The electrical activation of the left and right ventricles are described using a driver function and time varying elastance to model cardiac muscle activation. Separate driver functions are chosen for the left and right ventricles.

$$dri_L = A_L \cdot e^{(-b_L \cdot (t - \frac{period}{c_L})^2)} \quad (14)$$

$$dri_R = A_R \cdot e^{(-b_R \cdot (t - \frac{period}{c_R})^4)} \quad (15)$$

$$period = \frac{1}{heartrate} \quad (16)$$

where  $A_L = 1$ ,  $b_L = 2582.177$ ,  $c_L = 2.07$  and  $A_R = 1$ ,  $b_R = 91.5975$ ,  $c_R = 2.18$  for the left ( $L$ ) and right ventricles ( $R$ ).

In pulmonary embolism, if the embolus is large and associated with pulmonary artery obstruction, right ventricular dilation may occur and cause a leftward septum shift through ventricular interdependence [8,9]. Thus, the septum volume  $V_{sept}$  may be an important dynamic to capture in this case and it is described by a time-varying P-V relationship [1, 10]. The use of two different driver functions is physiologically justified, as the electric current spreads differently in both ventricles. More specifically, the cardiac activation pattern and times have been clinically observed to differ between the right and left ventricles [11, 12]. Finally, the activation function is also defined to change as a function of the heart period.

## 2.2 Integral Based Parameter Identification

An integral-based parameter identification method has been developed [3] that transforms the typically non-linear and non convex identification problem into a linear, convex problem using limited data and minimal computation. This method was extended in [13] to rapidly identify the porcine specific parameters from experiments. The available measured data for this study includes the pressure waveforms in the aorta ( $P_{ao}$ ), pulmonary artery ( $P_{pa}$ ) and the left and right ventricles ( $P_{lv}$ ,  $P_{rv}$ ), and the volumes of the left and right ventricles ( $V_{lv}$ ,  $V_{rv}$ ). However,  $P_{lv}$  and  $P_{rv}$  are not required for identification but are used for further validation.

Given the waveforms  $P_{ao}$ ,  $P_{pa}$  and  $V_{lv}$ ,  $V_{rv}$ , the integral identification process leads to a system of linear equations for the full CVS model [13]:

$$A \cdot \vec{x} = \vec{b} \quad (17)$$

$$\vec{x} = \left( L_{av}, L_{mt}, L_{tc}, L_{pv}, E_{es,lvf}, P_{0,lvf}, E_{es,rvf}, P_{0,rvf}, E_{ao}, E_{pa}, E_{vc}, E_{pu}, R_{av}, R_{mt}, R_{tc}, R_{pv}, P_{ao0}, P_{pu0}, P_{pa0}, P_{vc0}, R_{sys}, R_{pul} \right)^T \quad (18)$$

with  $\vec{x}$  being the solution vector of the parameters to be identified, which can be found by linear least squares. More details about this integral method and parameter definitions can be found in [3].

Note that in an Intensive Care Unit (ICU) setting, the waveforms  $P_{ao}$  and  $P_{pa}$  would be available with catheters, but the left ventricle volumes are not

typically measured. However stroke volume (SV) and global end-diastolic volume (GEDV) are readily available from the PiCCO monitor (Pulsion Medical Systems AG, Munich, Germany). Thus an estimate of the minimum and maximum volumes could be done based on a known blood distribution for the different compartments of the body [11]. An extension to the integral method [13] has shown that only the maximum and minimum pressures in the aorta and pulmonary artery and the volumes are sufficient for parameter identification. Future work will evaluate the importance of these volume estimates in the ICU and possibly consider the use of portable ultrasound probes [14] for more accuracy.

In this paper, the parameters are identified for each period of measured data during the porcine experiment of pulmonary embolism. Thus, time varying changes from the initial healthy state to the fully diseased state are captured providing close to continuous monitoring of the key hemodynamic responses.

### 2.3 Porcine Experiments and Data

Under the control of the Ethics committee of the Medical Faculty of the University of Liège, pulmonary embolization was induced in pigs with autologous blood clots [15]. The clots were injected every two hours with decreasing concentrations. Aortic pressure and pulmonary artery pressure are measured using micromanometer-tipped catheters (Sentron pressure-measuring catheter; Cordis, Miami, FL) while right and left ventricle pressures are measured using 7F, 12 electrodes (8-mm interelectrode distance) conductance micromanometer tipped catheters (CD Leycom, Zoetermeer, The Netherlands). This research uses data from 6 pigs in that study.

The conductance catheter technique is based on measuring time varying conductance of the blood in the ventricle. This conductance is approximately linearly proportional to the blood volume in the ventricle. To improve the accuracy, the ventricle is divided in several segments and the conductance of each segment is obtained by measuring the voltage between two adjacent electrodes of the conductance catheter. The ventricular volume is obtained as the sum of the segmental volumes [16].

## 3 Results

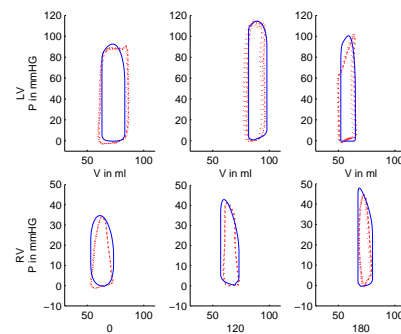
The parameter identification method is applied to the pig data. The identified parameters are used to rerun the CVS model and produce pressure and volume curves, which are then compared to the clinical data. This process is repeated in all the measured periods during the pulmonary embolism experiment using the pig's steady state response data. The results are shown for

one of the pigs in detail followed by a summary of the results in all pigs.

The main metric used to compare the simulated with measured data is the error in the maximum and minimum values in pressure and volume. Note that errors are not considered in the waveform shapes since there are dynamics which cannot be captured by the current minimal CVS model. For example, the diastolic notch cannot be captured as there is no atrium in the model. Thus, any error metric like the overall root-mean-squared-normalized error is not suitable as it will be corrupted by modelling error. Better waveform shapes could be obtained by adding further complexity to the model, but the philosophy in this research is to only add extra dynamics if a significant clinical benefit can be demonstrated. Future clinical trials will help determine what further dynamics are necessary for adequate diagnosis and therapy prediction.

### 3.1 Pig 2

Figure 2 presents the P-V loops for pig 2 at 0, 120 and 180 mins, showing that the model closely captures the clinically observed dynamics. The errors in the maximum and minimum pressures over all data have a mean of 2.2% and standard deviation of 1.7%. Similarly for the maximum and minimum volumes the mean error is 1.7% with a standard deviation of 1.3%. Figure 3 shows that the identified pulmonary and systemic vascular resistance ( $R_{pul}$ ,  $R_{sys}$ ) differ significantly between healthy and diseased state, as expected, with  $R_{pul}$  increasing by 89.98%.

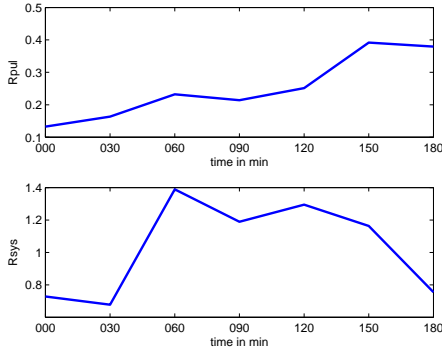


**Figure 2:** Pig 2: P-V Loops for left and right ventricle at 30, 120 and 180 mins (Dashed is clinical data and solid is identified model)

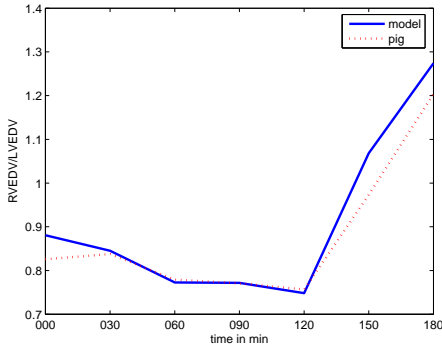
The model also captures the specific hemodynamic changes resulting from pulmonary embolism. The volume in the right ventricle ( $V_{rv}$ ) increases during pulmonary embolism due to the increased afterload, which causes right ventricle dilation. Figure 4 shows the time evolution of the left and right end-diastolic volume ratio (RVEDV/LVEDV) as an index for the expansion of the right ventricle during the experiment. As expected, this index increases.

Ventricular interaction changes are also captured,

where Figure 5 shows the time evolution of the mean value of the septum volume ( $V_{spt}$ ) over a cardiac cycle, decreasing from the beginning to the end of the experiment. This result agrees with the physiological fact that the overfilled right ventricle compresses the underfilled left ventricle during the embolization. Hence,  $V_{spt}$  decreases because it is defined as being part of the right ventricle volume [7, 10]. Finally, note that as the embolism grows and left ventricle volume decreases the systemic resistance,  $R_{sys}$ , increases in Figure 3, in the reflexive attempt to divert more blood to the heart. However,  $R_{sys}$  drops at the end likely due to the near death of the pig and very low stroke volume.



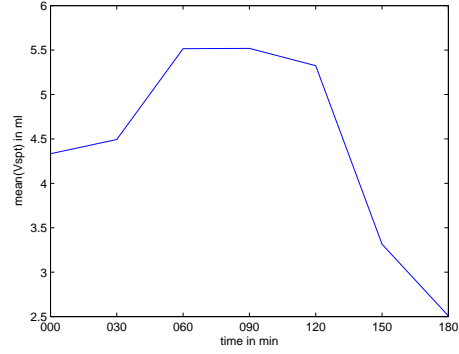
**Figure 3:** Pig 2: Pulmonary vascular ( $R_{pul}$ ) and systemic ( $R_{sys}$ ) resistance during pulmonary embolism experiment



**Figure 4:** Pig 2:  $RVEDV/LVEDV$ , simulated vs porcine data (dashed is clinical data and solid is identified model)

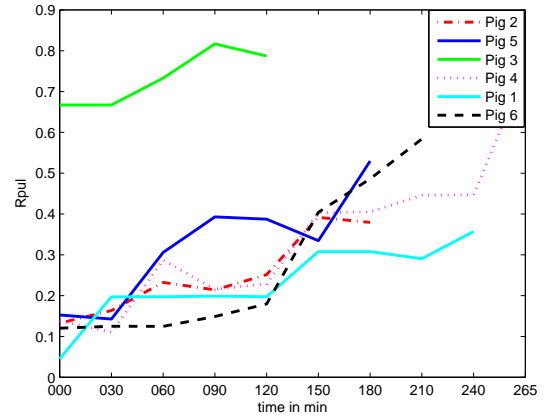
### 3.2 Summary of results in all 6 pigs

The total mean model response error for the pressures ( $P_{ao}$ ,  $P_{pa}$ ,  $P_{lv}$ ,  $P_{rv}$ ) and volumes ( $V_{lv}$ ,  $V_{rv}$ ) was  $2.22 \pm 2.17$  mmHg and  $2.37 \pm 2.01$  ml respectively showing that the model could accurately capture the measured clinical data. Table 1 shows the maximum percentage increase for pulmonary vascular resistance ( $R_{pul}$ ) and maximum percentage changes in systemic vascular resistance ( $R_{sys}$ ) and the contractilities ( $E_{es,lvf}$ ,  $E_{es,rvf}$ ) in the left and right ventricle during the pulmonary embolism experiment. The number of heart beat periods that are captured as well as the different points in time are shown. One of the goals is to capture rising pulmonary vascular resistance,  $R_{pul}$ ,



**Figure 5:** Pig 2: Mean septum volume  $V_{spt}$  during pulmonary embolism experiment

in this clinical case. Figure 6 shows  $R_{pul}$  over time for all 6 pigs.



**Figure 6:** Pulmonary vascular resistance ( $R_{pul}$ ) for all 6 pigs during the experiment

### 3.3 Right ventricular-vascular coupling

The ratio of contractility to afterload is used to measure right ventricular-vascular coupling where afterload is related to the pulmonary resistance  $R_{pul}$ . In the literature, afterload is commonly denoted  $E_a$  and is computed using a Windkessel model that takes into account the pulsatile nature of the blood [5, 17]. However a simpler quite accurate approximation for  $E_a$  is given by [17]:

$$E_a = \frac{R_{pul}}{T_s} \quad (19)$$

where  $T_s$  is the systolic time. The contractility is given by the model parameter  $E_{es,lvf}$ . Thus, a model-based measure  $E_{es,lvf}/E_a$  of coupling is computed based on the measured waveforms of  $P_{ao}$ ,  $P_{pa}$ ,  $V_{lv}$  and  $V_{rv}$ . Importantly, note that  $P_{lv}$  and  $P_{rv}$  are not used in the calculations as they are not typically measured in the ICU.

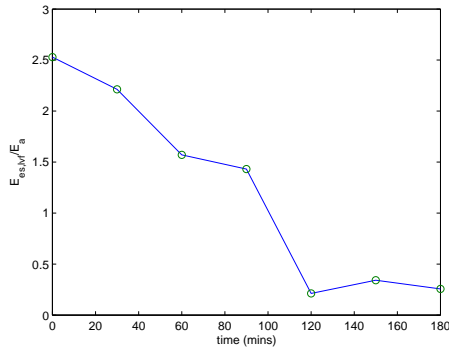
The model-based measure of coupling is compared with the standard highly invasive measure based on

Pig	# fitted periods	Time in min	%increase $R_{pul}$	%increase $R_{sys}$	%increase $E_{es,lvf}$	%increase $E_{es,rvf}$	%decrease $V_{spt}$
Pig 1	44	0-240	261.44	40.66	29.10	154.60	9.13
Pig 2	43	0-180	89.98	49.34	74.78	20.56	40.15
Pig 3	18	0-120	24.23	27.16	0.81	9.74	8.37
Pig 4	45	0-265	166.85	39.21	19.06	56.44	19.84
Pig 5	29	0-180	103.63	21.16	71.51	80.07	27.64
Pig 6	20	0-210	99.52	53.90	11.00	14.64	14.00

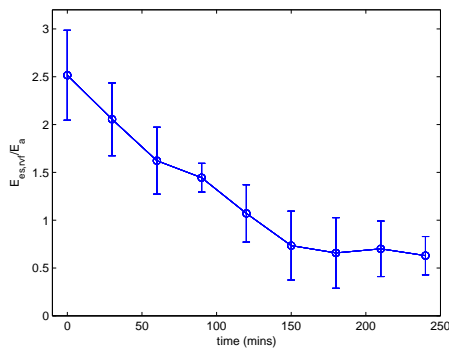
**Table 1:** CVS porcine specific parameters. Note that pig 3 only had limited data and insufficient time for the parameters to change significantly.

inflating a balloon catheter in the vena cava for a sufficiently short period, so that the pig's reflex responses don't have time to act. The result is a set of steeply descending pressure volume loops. The end systolic volume points are then computed by computing the maximum elastance (pressure/volume) on each PV loop. The best fit slope through these points is taken to be the contractility. For more details on this calculation see [5, 17].

Figure 7 shows the model-based coupling for pig 2 and Figure 8 summarizes the results over all pigs. The model-based measure starts at  $2.52 \pm 0.47$  and decreases to  $0.63 \pm 0.20$  at the end. This compares well to the invasive measure [17] which starts at  $2.78 \pm 0.16$  and decreases to  $0.72 \pm 0.24$  at the end.



**Figure 7:** Model-based right ventricular vascular coupling for pig 2



**Figure 8:** Model-based right ventricular vascular coupling for all pigs (mean  $\pm$  standard deviation)

The main result is that although the pigs preserve coupling reasonably well in the first 90 minutes, decoupling occurs at about 120 minutes where the contractility can no longer respond to the increasing afterload. Also, 90 minutes is the time the second injection is done which explains the sharp dip in the coupling form 90 to 120 minutes. The reason for the preservation of coupling in the initial period could possibly be explained by a dramatic increase in coronary flow [17]. The measured peak coronary before injection is  $27.1\text{ml/s}$  which increases to  $66.7\text{ml/s}$  30 minutes after injection. In other words, to maintain sufficient cardiac output by the coupling mechanism the oxygenation of the right ventricle is increased so that it is less efficient. Eventually the ability of the ventricle to increase contractility in response to increased afterload saturates which causes cardiac output to drop to a level which can no longer support life and the pig dies.

## 4 Discussion and Conclusions

The patient specific modelling methodology in this paper has been successfully validated on a porcine model of pulmonary embolism. A wide range of hemodynamics were captured over time and the integral method identified all model parameters with less than 5% error in clinical pressure and volume outputs. Pulmonary resistance significantly increased, septum volume decreased and the right ventricle expansion index increased, all consistent with known physiological response. The model was also shown to pick up reflex response where the pig increases systemic resistance to help restore blood pressure. However, near the end, when the pig is near death, systemic resistance ( $R_{sys}$ ) drops off. This last result is potentially a sign that the pig can no longer regulate hemodynamics effectively.

The patient specific modelling approach enabled continuous monitoring of right ventricle pulmonary vascular coupling, and was shown to compare well with a highly invasive vena cava occlusion maneuver. This is an important example of how common measurements in the ICU can be aggregated into a more clinically useful form that relates directly to mechanisms leading to heart failure. The overall result is a model-based sensor which can adapt to wide ranges

of hemodynamics and shows potential for real-time diagnosis and therapy assistance in critical care.

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